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Plasma VEGF as a marker for the diagnosis and treatment of vasculitic neuropathy

Vasculitic neuropathy is treatable with immunotherapy. However, histological evidence of vasculitis is not always obtained from nerve and muscle biopsies.[1] In particular, in cases of non-systemic vasculitic neuropathy showing no or minimum abnormal findings in serological tests, negative biopsy results cause considerable difficulty in the diagnosis.[1]

Vascular endothelial growth factor (VEGF) is a potent, multifactorial cytokine.[2] VEGF is derived from endothelial cells and pericytes in response to hypoxia, and induces angiogenesis and microvascular hyperpermeability through its binding to VEGF receptors.[2] Vascular involvement by vasculitic neuropathy results in hypoxia. It was reported that VEGF was overexpressed in vasculitic lesions in biopsied sural nerves, and that plasma VEGF levels were found to be raised in dermatomyositis with peripheral neuropathy.[3] These findings suggest that VEGF levels may be increased in patients with vasculitic neuropathy. Although an increase in plasma or serum VEGF concentrations has been reported in some patients with systemic vasculitis,[3] there have been no studies to evaluate plasma VEGF in a series of patients with vasculitic neuropathy. With respect to VEGF levels in neuropathies, a marked increase in serum levels was reported in the Crow-Fukase (POEMS) syndrome.[4] In addition, alterations in VEGF are associated with cancer and diabetes mellitus, and VEGF is involved in the angiogenesis of these diseases.

In this study, we investigated the plasma VEGF concentrations in patients with vasculitic neuropathy in comparison with other neuropathies. After obtaining informed consent, samples were obtained from five patients with vasculitic neuropathy confirmed by muscle or sural nerve biopsies. They all presented with neuropathy as a cardinal manifestation, and included three patients with polyarteritis nodosa, one with vasculitic neuropathy associated with Sjögren syndrome, and one with non-systemic vasculitic neuropathy. None of the patients were on drug treatment at the time of sampling. After disease remission was achieved by treatment with corticosteroids or other immunosuppressants, we analysed plasma VEGF again in three of the patients, including two with polyarteritis nodosa and one with Sjögren syndrome. As a control group, we used plasma from 18 age matched healthy volunteers, eight patients with Guillain-Barré syndrome, five with chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), and seven with amyotrophic lateral sclerosis, after obtaining informed consent. Patients with diabetes mellitus or cancer were not included in the study.

Venous blood was sampled into an EDTA tube with minimal stasis. The sample was centrifuged and the plasma VEGF concentration was determined by a quantitative sandwich-enzyme immunoassay technique using a Quantikine kit (R&D Systems, Minneapolis, Minnesota, USA). As VEGF is secreted by platelets in the clotting process,[5] we measured plasma samples, not sera, to evaluate the circulating VEGF level precisely.

Differences between the groups were tested by the Kruskal–Wallis test and the Mann–Whitney U test. Differences were considered significant when the probability (p) value was <0.05. Significance tests for group differences were computed with StatView v5.0 (SAS Institute, Cary, North Carolina, USA).

The mean (SD) plasma VEGF concentrations in patients with vasculitic neuropathy (303 (182) pg/ml) were significantly higher than in the healthy controls (30.9 (31.7) pg/ml) ($p<0.01$) as well as in patients with Guillain-Barré syndrome (85.7 (57.3) pg/ml) ($p<0.05$), CIDP (49.9 (48.3) pg/ml) ($p<0.05$), and amyotrophic lateral sclerosis (88.1 (55.7) pg/ml) ($p<0.05$) (fig 1). There was no statistical difference in plasma VEGF concentrations between healthy controls and patients with CIDP, Guillain-Barré syndrome, or amyotrophic lateral sclerosis. The plasma VEGF concentrations in patients with vasculitic neuropathy before treatment (423 (97.1) pg/ml) decreased significantly after successful treatment with corticosteroids or other immunosuppressants, to 150 (114) pg/ml ($p<0.05$). One case with polyarteritis nodosa and the patients with vasculitic neuropathy associated with Sjögren syndrome had a marked decrease in plasma VEGF after treatment (from 461 to 91.3 pg/ml and from 496 to 77.8 pg/ml, respectively). In the other patient with polyarteritis nodosa, the plasma VEGF levels decreased mildly, from 313 to 281 pg/ml.

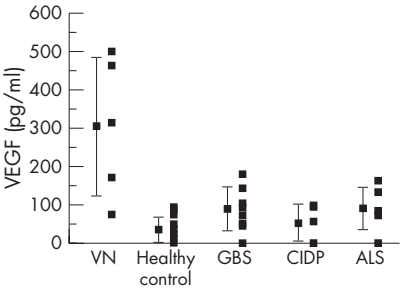

Figure 1 Plasma levels of vascular endothelial growth factor (VEGF) in patients with vasculitic neuropathy (VN), healthy controls, Guillain-Barré syndrome (GBS), chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), and amyotrophic lateral sclerosis (ALS).

COMMENT

Our results indicated that increased plasma VEGF could be a useful marker for the diagnosis of vasculitic neuropathy and for monitoring a therapeutic effect.

This is the first report to show a significant increase in plasma VEGF levels in patients with vasculitic neuropathy compared with other neuropathies. As our patients with vasculitic neuropathy did not have cancer or diabetes mellitus, and as the plasma VEGF concentrations were significantly decreased after treatment, we consider that VEGF would be secreted into blood by the vasculitic lesions in this conditions. We could find no significant increase in plasma VEGF levels in CIDP, Guillain-Barré syndrome, or amyotrophic lateral sclerosis. Vasculitic neuropathy may present with clinical manifestations similar to CIDP or other peripheral neuropathies.[1] The increase in plasma VEGF could be a helpful marker to distinguish vasculitic neuropathy from CIDP and other peripheral neuropathies in such patients.

Although our results indicate the potential value of plasma VEGF as a marker in the diagnosis and treatment of vasculitic neuropathy, the significance of the results is limited by the relatively small number of patients. Further studies with a larger study population are necessary to confirm our results.

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Acute aspiration pneumonia due to bulbar palsy: an initial manifestation of posterior fossa convexity meningioma

False localising signs of intracranial lesions are defined as signs not generally associated with disturbances of function at the site of

the lesion.[1 2] An intracranial tumour which has not metastasised may give rise to focal signs of disordered nervous function at a distance from itself in a number of ways. Even though these neurological signs are labelled as false localising signs, it is important to be aware that such signs are in no way "false".[3] Various cranial nerve palsies have been reported as false localising signs, with the sixth cranial nerve being the most common.[1] According to Gassel, ninth to 12th cranial nerve palsies never provide false localisation.[1] Since Dodge reported the first case of false localising sign involving the lower cranial nerve, only two cases have been reported in the literature.[4] We report a third case of false localising sign involving the left ninth and 10th cranial nerves.

A 29 year old man presented to the medical department of our hospital with history of hoarseness of voice of 15 days duration, dysphagia of 1 week duration, and cough with expectoration and respiratory distress of 2 days duration together with history of fever. On examination, he was febrile, with a pulse of 100 bpm and blood pressure of 120/80 mm Hg. Respiratory examination revealed bilateral coarse crepitations. Neurological examination revealed absent gag reflex on the left side with deviation of the palate to the right side without any other neurological deficit. Indirect laryngoscopic examination revealed paralysis of left vocal cord.

Haematological examination revealed haemoglobin (Hb) 13.6%, a WBC count of 16 800/mm, and an erythrocyte sedimentation rate (ESR) of 120 mm/h. Chest *x* ray of the patient revealed bilateral pneumonitis. He was treated with antibiotics according to culture sensitivity. He progressively improved and was discharged. At discharge, he had persistent hoarseness of voice and vocal cord palsy on the left side. About 4 weeks later he presented with a history of bifrontal headache and was referred to our department. Neurological examination revealed bilateral papilledema and left palatal palsy with absent gag reflex. Other cranial nerves were normal. Motor and sensory system examination was normal. Occasional swaying to the left side on tandem walking suggested involvement of the cerebellar system. In view of these findings, a left posterior fossa mass lesion involving the lower cranial nerves such as a schwannoma was suspected. However, magnetic resonance imaging (MRI) of the brain revealed a large isointense homogenously enhancing mass lesion attached to the convexity dura (fig 1). It also revealed evidence of herniation of the cerebellar tonsils below the margin of the foramen of magnum and anterior displacement of the cerebellum causing stretching of the lower cranial nerves on the left side. The patient underwent midline suboccipital craniectomy and total excision of the lesion. The cerebellum was found compressed and deeply indented by the tumour. Postoperatively he improved neurologically. His gag reflex and palatal movements progressively improved and he was asymptomatic at 2 month follow up.

False localising signs are unexpected neurological deficits and reflect pathology distant from the expected anatomical locus. Prominent false localising signs are less common today, as diagnosis is usually made at an early stage.[4] Cranial nerve involvement as a false localising sign is found in 12.5% of cerebral tumours.[2] According to Gassel, false localising signs are more common in patients with signs of raised intracranial pressure. Due to the long intracranial course, sixth cranial nerve palsy is commonly associated with supratentorial mass lesions as a false localising sign.[1] Most reports described single cranial nerve disturbance as a false localising sign. Rarely have multiple cranial nerve palsies been reported as false localising signs.[4 5]

Ehni proposed various mechanisms responsible for false localising signs. These include: (i) general compression of a nerve having a long course; (ii) meningitis; (iii) oedema and gliosis; (iv) metastatic deposits; (v) infarctions at a distance from the primary lesion due to occlusion of a vessel by a neoplasm or by cerebral herniation through a dural aperture; (vi) gross brain displacement involving the brainstem and causing traction of cranial nerves and kinking of cranial nerves over vessels; and (vii) brain stem shifting to the opposite side causing tentorial notching, pressure at the rim of the foramen magnum, pressure at points of emergence of cranial nerves, and involvement of the corticospinal tract.[6] Gassel pointed out that false localising signs are commonly associated with intracranial meningiomas as they are discrete tumours that tend to compress and displace the brain rather than infiltrate cerebral tissues.[1] He also commented upon the rigidity of the bony skull and its dural compartments, as well as the outcome of pressure within the skull causing movement of parts of the brain towards the tentorial opening and foramen magnum resulting in herniation pressure on various blood vessels.[1] O'Connell suggested that displacement of the brainstem by the tumour results in slackening of the horizontally directed nerves such the seventh to 11th cranial nerves and stretching of the anteriorly directed nerves such as the fifth and sixth around the lateral margin of the dural foramen.[7] Matsuura and Kondo proposed that displacement rather than rotation of the brainstem, causing compression and/or angulation of the affected nerve rather than stretching or traction, is the most significant factor for inducing contralateral trigeminal neuralgia and hemifacial spasm.[5] However, according to Haddad and Taha, rotation of the brainstem shifts the basilar artery or loop of its branches close to the trigeminal nerve at its root entry zone and causes trigeminal neuralgia.[8]

Most cranial nerve dysfunctions presenting as false localising signs appear as hypoactive dysfunctions.[1 6] Rarely has hyperactive dysfunction syndrome involving the cranial nerve, such as trigeminal neuralgia or hemifacial spasm, been reported in the literature.[5 8] False localising sign involving lower cranial nerves is extremely rare with just two cases reported in the literature.[4] Maurice-Williams proposed two mechanisms causing lower cranial nerve palsy: firstly, cerebellar hemisphere impacting the foramen magnum, causing reaction and oedema and thereby compression of the lower cranial nerve and secondly, displacement of the cerebellum to the contralateral side, forcing the brainstem to the ipsilateral side and thus exerting traction on the contralateral lower cranial nerve.[4] The case reported here involved a large cerebellar convexity meningioma causing cerebellar herniation downwards into the foramen magnum and anteriorly into the lateral cerebello-medullary cistern which resulted in stretching of the lower cranial nerves. The cranial nerve function improved following excision of the tumour. Awareness of the possibility of false localising signs and the conditions in which they are most likely to occur is very important as they may be indicative of serious life threatening pathology within the neural pathway.[3]

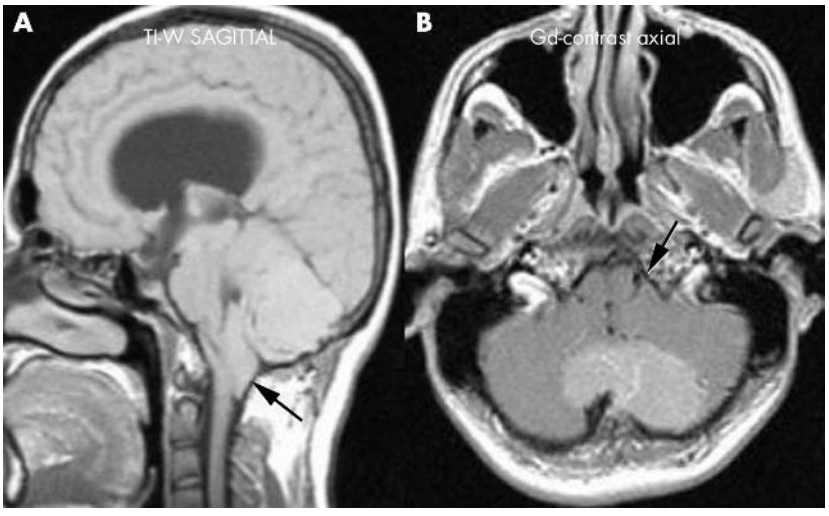

Figure 1 MRI of the brain. (A) Sagittal section shows herniation of the tonsils below the foramen magnum due to an isointense mass lesion (arrow). (B) Axial T1 weighted image showing isointense mass lesion, enhanced homogenously with gadolinium, causing compression of the cerebellum and anterior displacement of the cerebellum into the lateral cerebello-medullary cistern resulting in stretching of the lower cranial nerves (arrow).

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Acquired Chiari 1 malformation and syringomyelia following lumboperitoneal shunting for pseudotumour cerebri

An important but not widely recognised complication of lumboperitoneal shunting is the development of a Chiari 1 deformity and syringomyelia. We present a case of a patient who developed symptomatic cerebellar tonsillar descent and syrinx formation following treatment of pseudotumour cerebri with lumboperitoneal shunting.

Case report

A 31 year old woman was diagnosed with pseudotumour cerebri following development of headaches, loss of vision, and papilloedema, in association with a cerebrospinal fluid (CSF) opening pressure of 36 cm H_2O. Cranial imaging showed an attenuated ventricular system and no other abnormality. In particular, the posterior fossa was satisfactory in appearance. She was treated with lumboperitoneal shunt insertion, with resolution of her symptoms.

Twelve months later, the patient reported a 6 month history of left hemisensory loss, left arm weakness, and unsteadiness. Neurological examination revealed wasting and reduced power of the intrinsic muscles of the left hand, and left-sided hyperaesthesia to pin-prick. Magnetic resonance (MR) imaging showed the development of cerebellar tonsillar descent and syringomyelia throughout the cervico-thoracic spinal cord. The patient underwent insertion of a low pressure ventriculoperitoneal shunt and removal of the lumboperitoneal shunt, with subsequent symptomatic improvement. There was, however, no resolution of the syrinx on follow up MR imaging.

Discussion

The development of cerebellar tonsillar descent is a recognised but rarely reported complication following lumboperitoneal shunting,[1–5] usually in the treatment of communicating hydrocephalus.[1 3 5] It has been reported to occur in a large proportion of paediatric patients undergoing this procedure, with Chumas *et al* reporting a 70% incidence in this age group,[1] but its incidence in the adult population is undefined. The development of secondary syringomyelia appears to be much less common, with the above paediatric patients reporting an incidence of syrinx formation of 4%. The development of Chiari 1 and syringomyelia formation following lumboureteral shunting for the treatment of pseudotumour cerebri is recognised but has been less commonly reported.[2 4 5]

There is a small number of papers reporting chiari development following lumbar shunting for communicating hydrocephalus in children, but only two case reports of syringomyelia formation.

The association of syrinx formation and cerebellar tonsillar descent through the foramen magnum is well described,[6] and is postulated to occur as a consequence of a cranial-spinal CSF pressure gradient and diversion of CSF down the central canal of the spinal cord rather than over the cerebral convexities.[3 4 6] It would seem remarkable that this complication is not seen more commonly in the treatment of pseudotumour cerebri.

The non-resolution of the syrinx, in our case following lumboperitoneal shunt removal, is consistent with other workers' experiences, although resolution has been reported in one instance.[7]

In conclusion, we describe the development of Chiari 1 deformity and syrinx formation as an important but otherwise poorly recognised complication of lumboperitoneal shunting in patients with pseudotumour cerebri.

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Effect of posture on levels of arousal and awareness in vegetative and minimally conscious state patients: a preliminary investigation

Moderate to severe brain injury is estimated to occur in 25 individuals per 100 000 population every year. Of these, 10–20% never fully regain consciousness but remain in a vegetative or minimally conscious state.[1] Patients in the vegetative state may appear at times to be wakeful, with cycles of eye closure and eye opening resembling those of sleep and waking, but show no sign of awareness or of a functioning mind.[2] In contrast, patients considered to be in a minimally conscious state are said to show inconsistent but definite evidence of awareness despite profound cognitive impairment.[3]

At present, the pathophysiology underlying the vegetative and minimally conscious states is unclear, a standard treatment approach is lacking, and very little has been discovered to advance rehabilitation techniques. It is widely acknowledged that active rehabilitation should begin early in the intensive care setting, and should be applied to all patients (including those who remain mechanically ventilated). However, this is not yet routine practice. Several reports have highlighted the generic benefits of early rehabilitation,[4] however, the benefits of specific interventions remain to be demonstrated. Over the last year, our group has investigated the effects of postural change on levels of arousal and awareness.

A total of 12 patients (eight men, four women; mean age 49 years, range 19–71) classified as either vegetative (n = 5) or minimally conscious (n = 7) according to international guidelines[2 3] were assessed using the Wessex Head Injury Matrix (WHIM), a 62 point score, which records the recovery of behaviours in brain injured patients.[5] Patients were assessed lying in bed, during a 20 minute period of standing using a tilt table at 85°, and again while lying in bed. During the observations blood pressure was measured using an oscillometric cuff. The observations were repeated over a one week period, and the median highest ranked behaviour and median total number of behaviours observed were recorded. The local research ethics committee approved all investigations. Informed assent was obtained from the next of kin.

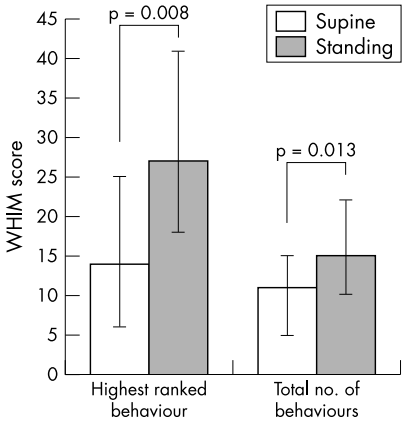

Figure 1 The median highest ranked behaviour and total number of behaviours observed in the lying and standing positions for both vegetative and minimally conscious patients. The highest rank (p = 0.008) and total number of behaviours (p = 0.0013) observed increased significantly in the standing position. Error bars indicate the interquartile range. WHIM, Wessex Head Injury Matrix.